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Identification and Mitigation of Risks using Quality Risk Assessment Tools for Formulation Development of Pazopanib HCl Extrudates by using HME Technique: A Systematic QbD Approach

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ABSTRACT

Introduction: Pharmaceutical development ensures to design a valued product and robust manufacturing process to consistently deliver intended performance. It is necessary to recognize that quality cannot be tested into drug products but it should be built in during formulation design and development.

Pazopanib HCl is a protein kinase inhibitor molecule approved by USFDA and European agencies for the treatment of renal cell carcinoma (RCC) patients and other renal malignancies, but it has very poor aqueous solubility and drug release. Therefore, it is essential need to improve the solubility and in vitro dissolution characteristics.

Objective/Aim: The main objective of this study was to prepare stable Pazopanib HCl extrudates (PZP-Ex) by using Quality by Design (QbD) approach.

Method: Pazopanib HCl extrudates (PZP-Ex) was manufactured using hot melt extrusion technique. Initially, the quality target product profile (QTPP) and critical quality attributes (CQAs) were identified and then risk assessment was done using heat map and failure mode and effect analysis (FMEA) approach. A full factorial design (FFD) was used to study impact of two continuous variable i.e., level of polymer, milling speed and one categorical (milling screen type) factor on particle size distribution (PSD), disintegration time and dissolution of extrudates.

Results: The significance (p) value for studied response variables i.e., percent retention on 40 mesh ASTM sieve (420 µ), disintegration time and percent drug release in 15 min were 0.006, 0.0243 and 0.0355 respectively from the actual by predicted plot which signifies that the model is significant. The polymer to drug ratio has significant impact on drug release and disintegration time of extrudates.

Conclusion: Pazopanib HCl extrudates were successfully prepared by HME technique. Critical formulation and process parameters such as polymer to drug ratio, milling screen size and milling speed were optimized using FFD design.

Key Words: CQAs, FMEA, Heatmap, QbD, QTPP, Risk management

INTRODUCTION

In the 21st century, "Risk Management Principles" are most commonly and effectively employed in various areas of business operations such as finance, safety, public health including biological and pharmaceutical research domain.[1] The main objective of pharmaceutical development is to design a quality product and its manufacturing process to deliver consistently the intended performance of the drug product.[2]

In past decade, the traditional quality by testing (QbT) approach was used to ensure the quality of drug products by checking it against the regulatory specifications.[3] Quality by design (QbD) is described in ICH Q8, Q9 and Q10 guidance documents. QbD principles promote systematic, scientific knowledge-based development for continuous improvement of pharmaceutical drug products. The product or process knowledge, risk assessment and its management, quality management system (QMS) along with the use of process analytical technology (PAT) are tools for successful product development.[4] Now a days, pharmaceutical industries are more focusing to develop and integrate the quality systems within organizations practices; hence, quality risk management is a valuable and main component of an effective quality system.[5]

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Pazopanib HCl is a potent tyrosine kinase inhibitor that inhibits angiogenesis through the VEGFR receptor and blocks tumor growth. This drug molecule has been used in the treatment of renal cell carcinoma and other malignancies. It is a poorly water soluble and highly permeable class II drug of Biopharmaceutics Classification System (BCS). The recommended maximum daily dose of Pazopanib HCl is up to 800 mg, administered as 4 tablets of 200 mg strength.[6] The goal of this study was to identify, ranking and mitigation of process associated risks to the drug product critical quality attributes(CQAs) during the development of Pazopanib HCl HME extrudates using QbD elements and risk management tools.[7]

It is hypothesized that HME polymer physicochemical properties will have a major impact on the qualities of drug extrudates, since the HME polymer is major component. The aim of the present study was to optimize polymer to drug ratio to get maximum miscibility and obtain a Pazopanib HCl extrudates (PZP-Ex) with faster disintegration time and drug release. The critical process parameters (CPPs) such as milling screen size and milling speed during extrudate preparation and its impact on extrudates PSD, disintegration, and dissolution time were also studied.

Commonly used material such as Affinisol HPMC as HME polymer and poloxamer 188 as plasticizer were used in current study. The outcomes from this study may provide a way forward to other researchers in developing HME extrudates with better compressibility and desired attributes, such as faster disintegration time and dissolution.

MATERIALS AND METHODS

Materials

Pazopanib HCl active pharmaceutical ingredient was gifted from Sun Pharmaceutical Industries Ltd., Gurgaon, India. The cellulosic polymer Affinisol HPMC HME 15LV was donated by Dupont (Nutrition and Biosciences, USA). Other ingredients such as Poloxamer 188 were obtained from BASF Corporation (Mumbai, India). All other chemicals and solvents used in this study were of analytical grade.

Methods

QbD elements and risk assessment procedure

The main component of product development by QbD are quality target product profile (QTPP), critical quality attributes (CQAs),design of experiments (DoE), risk assessment and control strategy.[8] Control strategy is generally defined based on the scientific knowledge gained during product development and experimentation, which establish the relationship between formulation and process variables that must be controlled to develop high quality product.[9,10] Quality risk assessment process is utilized for identification, analysis, evaluation and mitigation of risks related to intermediate in process quality assurance (IPQA) and during production check quality assurance.[11] A general process flow for quality risk assessment (QRA) are described in figure1.

Figure 1: Quality risk assessment process flow.

Preparation of Pazopanib HCl HME Extrudates (PZP-Ex)

The Pazopanib HCl extrudates (PZP-Ex) was manufactured as per below mentioned formula in Table 1. Initially Affinisol HPMC 15 LV polymer, poloxamer 188 and pazopanib HCl drug were mixed in rapid mixer granulator for 5 minutes at slow impeller speed. Then prepared premix was extruded using a hot melt extruder instrument. Hot melt extrusion were carried out using co-rotating twin-screw extruder (Thermo-scientific) fitted with various screws containing kneading elements at 30° and 60° orientation. The feed rate of the premix material and the screw speed were kept constant at 2 g/min and 100 rpm respectively. The barrel temperature was kept as (100/180/180/180/180 °C) for different trials. The extrudates were kept at room temperature prior to milling operation. A Quadro Comil (Fitzpatrick) was operated at defined speed with forward knives fitted with suitable size screen to mill the extrudates. The 16 # ASTM (1204 µm) to 20 # ASTM (850 µm) powder fraction was collected and further used for disintegration and dissolution testing.

Table 1: Composition of Pazopanib HCl Extrudates

Ingredients	Functional role	Quantity (mg)
Intragranular		
Pazopanib HCl	Active	200.000
Affinisol HPMC 15 LV	Polymer	400.000
Plasticizer	Plasticizer	40.000
Total Weight		640.000

Heat map

In heat map, the level of risk (low/medium/high) is assigned through colour. Risk coding is based on the prior scientific knowledge including experimental outcomes and justification is provided for assigned risk in each cell considering severity. The green colour has been coded for low risk, yellow for medium risk and red for high risk.[12]

Failure mode and effect analysis (FMEA)

FMEA is an exhaustive technique that can help us to determine the potential failure modes and its

causes, potential failure effects, severity rank of the failure effect, occurrence rank of the failure, current detection mode and its failure rate. Hence, risk assigned in heat map and FMEA shall be mitigated based on the scientific rationale and through execution of experiments.[13] Refer below tables for risk level, RPN range, colour criteria and scoring criteria for failure mode and risk analysis (Table 2, 3).

Table 2: Risk level with risk priority number (RPN) range.

RPN range	Colour Criteria	Risk rank	Risk level
1-9	Green	Low	Acceptable
10-27	Yellow	Medium	Undesirable
28-125	Red	High	Unacceptable

Table 3: Scoring criteria for failure mode and risk analysis.

Score	Severity of impact (S)	Occurrence of potential cause (O)	Detection failure rate
1	No impact on DPCQAs	Not happened (failure Unlikely)	Process failure can be detected before process/ unit operation
2	No significant impact on DP-CQAs. Online solution is feasible & root cause is well understood	No prior information available(remote possibility of occurrence)	Process failure can be detected during process/ in-process controls available
3	Impact on quality attributes but action/ reworking required	No prior information available (occur periodically)	Process failure can be detected readily after process/in-process controls available
4	Impact on DPCQAs (batch failure)	No prior information available (fair chances of occurrence)	Controls have poor chances of detecting failure/in-process controls to be established
5	Batch failure irreversibly and product recall. Hazardous for personnel involved	Prior information available (occur frequently)	No detection/ no control available to detect failure

Experimental trials

DoE approach was employed for systematic optimization of formulation and process variables during Pazopanib HCl extrudates (PZP-Ex) preparation. A full factorial design (FFD) was selected with three factors and two levels (low and high) as shown in Table 4. The polymer to drug ratio and milling speed are continuous variable and evaluated at the ratio of 0.5:1 to 2:1 and 1200 -2400 rpm respectively. Whereas, milling screen size is a categorical factor and studied the impact of 40G and 50G milling screen on granule characteristics, disintegration time and percent drug release.

Table 4: Factors and response studied

Factor		Level	
		Low (-1)	High (+1)
A	Polymer to drug Ratio	0.5:1	2:1
B	Milling screen	40G	50G
C	Milling Speed	1200	2400
Response		Target Range	
R1	Disintegration time	Not more than 15 min	
R2	% Retention on 60 mesh sieve	20 to 40%	
R3	Amount of % drug release (15 min)	Not less than 80% in 15 min	

RESULTS

QbD elements and risk assessment procedure

Based on the clinical and pharmacokinetic characteristics as well as the physicochemical characteristics requirements, QTPP and CQAs elements were defined to guide the development of Pazopanib HCl extrudates by HME technique (Table 5).

Table 5: Quality target product profile and CQAs of Pazopanib HCl Extrudates

QTPP Elements	Target	Justification
Dosage form and Design	HME Extrudates	Needed to obtain faster dissolution.
Route of administration	Oral	Same route of administration as marketed reference product and easy to administer.
Dosage strength	200 mg	Same strengths as reference product.
CQAs Elements	Target	Justification

Disintegration Time	Faster disintegration (within 15 mins)	Faster disintegration of extrudates will help to quick release of drug and would lead to achieve faster absorption and higher bioavailability.
Dissolution	Faster dissolution (more than 85% in 15 mins)	Faster dissolution to achieve therapeutic benefits. Failure to meet the dissolution specification can affect bioavailability. Both formulation and process variables may affect the dissolution profile.

QTPP: quality target product profile; CQAs: Critical quality attributes

Preparation of Pazopanib HCl HME Extrudates (PZP-Ex)

Pazopanib HCl extrudates were manufactured using hot melt extrusion technique, which are having unit operations such as sifting, mixing, extrusion and milling. Process map are described in below figure (figure 2).

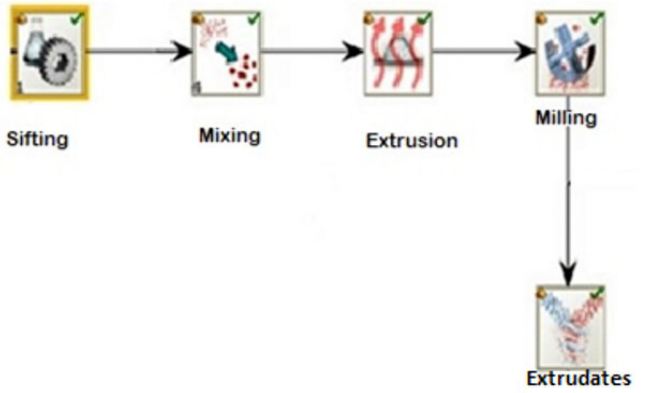

Figure 2: Process map for preparation of Pazopanib HCl HME Extrudates (PZP-Ex).

Heat map

Heat map is a systematic approach employed to understand and prioritize the risk elements. In order to evaluate the impact of each variable on DPCQAs, risk coding is done.

In heat map (Table 6), variable location, parameter location and drug product CQAs is listed in the header row. For each variable, the cell is filled with designated colour for the assigned risk and justification updated. The justification is provided based on the severity.

Table 6: Heat map for manufacturing process of Pazopanib HCl Extrudates

Variable location	Parameter location	% granules/Extrudates Retention	DT	Dissolution
Sifting	Sieve Size	Sifting process is unlikely to affect the in-process CQAs and DPCQAs. Sifting is carried out to avoid lumpy mass which may have in raw material. Hence, risk is kept as low.		
Dry mixing	Dry mixing time	Dry mixing in rapid mixer granulator is unlikely to affect the in-process CQAs and DPCQAs. Hence, risk is low.		
Hot Melt Extrusion	Polymer to drug ratio	It is likely to affect extrudates characteristics and granulometry. Hence risk is medium.	Amount of polymer amount in extrudates may likely to affects the DT and % drug release. Hence, risk is high.	
Milling	Screen size and Speed	The milling parameter such as screen size and milling speed can affect the size/density of the granules, coarse to fine ratio and ultimately particle size distribution. Particle size distribution of granules may further affect DT, dissolution of drug product. Thus, risk is high.		

CQAs: critical quality attributes, DPCQAs: drug product critical quality attributes

Failure mode and effect analysis (FMEA)

Failure mode and effects analysis is a structured and systematic process to identify potential possible failures in drug product. Initial FMEA for manufacturing process of pazopanib HCl extrudates are summarized in Table 7.

Table 7: Initial failure mode and effect analysis (FMEA) of manufacturing process for pazopanib HCl extrudates (PZP-Ex)

Variable location	Variable	Failure mode	Rationale for potential impact on DPCQAs	S	Potential cause(s) of failure mode	O	Current detection mode of the cause	D	RPN
HME Formula	% Polymer Level	Excessive quantity	Higher level may likely to slower release from extrudates	4	Quantity not optimized	3	Need to establish	2	24
Milling	Screen size	Not proper	Improper selection of screen will generate undesired granulometry and likely to impact the drug product dissolution.	4	Not optimized	3	Need to establish	3	36
Milling	Speed	Not defined	Too high or low speed may affect extrudates fractions and likely to impact DT, Dissolution	3	Not fixed	2	Need to establish	2	12

S-Severity, O- Occurrence, D- Detectability, Risk priority number (RPN) = S × O × D, DPCQAs- Drug product CQAs

Experimental trials

Based on the initial risk assessment for formulation components, experimental trials were conducted to evaluate the risk of processing steps. Experimental trial matrix and trials outcomes depicted in table 8. All statistical analysis has been carried out using JMP Software (by SAS, version 16).

Table 8: Trial matrix with experimental results for studied responses.

Run No.	Factors and responses					
	Polymer: Drug	Milling screen	Milling speed	%Retention on 40 mesh sieve	Disintegration time (s)	Dissolution (15 min)
1	0.5:1	40G	1200	32.24	65	85
2	0.5:1	40G	2400	31.37	105	67
3	0.5:1	50G	1200	38.45	90	81
4	0.5:1	50G	2400	37.52	135	75
5	2:1	40G	1200	43.21	83	69
6	2:1	40G	2400	44.15	162	78
7	2:1	50G	1200	48.26	124	72
8	2:1	50G	2400	47.88	186	84
9	1:1	40G	1800	39.41	118	71
10	1:1	50G	1800	41.73	149	66

The particle size distribution of extrudates was carried out using sieve shaker and percent retention on 40 mesh sieve size calculated. The 16 # ASTM (1204 µm) to 20 # ASTM (850 µm) extrudates fraction was collected and further used for disintegration and dissolution testing. The disintegration time is also an important in-process material attribute and were carried out in water (n=6) at 37±2^{0}C with sinker using disintegration test apparatus. Disintegration test of 16-20 # fraction extrudates material was carried out by holding the material in 40# stainless steel sinker. The percent drug release at 15 min time point in pH 6.8 phosphate buffer, 900 ml, type I (basket) was carried out and samples analysed using validated HPLC method.

Statistical Outcomes of Experimental Trials

The DoE trials with responses were analysed in JMP software (version 16.0) through "fit Model" approach. Based on the ANOVA and regression analysis, p value and R square value were observed from the "Actual predicted plot" for each response and recorded in table 9.

Table 9: R square and p value from actual by predicted plot

Response	R square	p value
% Retention on 60 mesh sieve	0.99	0.006
Disintegration time	0.97	0.0243
Amount of % drug release (15 min)	0.96	0.0355

The sorted parameters (Table 10) and prediction profiler (Figure 3) indicated the impact of polymer to drug ratio level, milling screen and milling speed and its interaction terms on extrudates characteristics such as particle size distribution, disintegration time and dissolution. The sorted parameters for each term are summarized below:

Table 10: Sorted parameter estimates for responses

Term	% Retention on 40 mesh sieve		Disintegration time		Dissolution (15 min)	
	Estimate	Prob>|t|	Estimate	Prob>|t|	Estimate	Prob>|t|
Polymer: Drug Ratio	5.49	0.0008*	28.25	0.0064*	11.25	0.0058*
Milling screen size	2.346	0.0070*	20.0	0.0168*	5.25	0.0460*
Polymer: Drug ×Milling screen size	0.4475	0.3410	15.1	0.0264*	3.3	0.1036
Polymer: Drug × Milling speed	0.295	0.5107	7.0	0.1885	2.0	0.2985
Milling screen size × Milling speed	0.1725	0.6928	1.5	0.7404	1.5	0.4162
Milling speed	0.155	0.7218	1.25	0.7818	1.0	0.5750

Impact of polymer to drug ratio: Based on the sorted parameters and prediction profiler (figure 3) it can be concluded that polymer level has significant impact on studied responses and p value was found < 0.05. At optimum polymer to drug ratio (1:1), model predicted the % retention on 40#, DT and dissolution at 15 mins about 38.1%, 99 secs (1 min 39 secs) and 81.3% respectively.

Impact of milling screen size: Based on the *p* value from the sorted parameter results as shown above in the table 10, milling screen size has significant impact on all the studied responses. As per the prediction profiler, 40G screen size has obtained the finer granules in comparison to the 50G obtained granules.

Impact of milling speed: Based on the sorted parameters it can be concluded that milling speed has no significant impact on studied responses and p value was found > 0.05. However, from prediction profiler it was observed that% drug release decreased by decreasing the milling rpm. This might be due to slight less fine formation at lower milling speed.

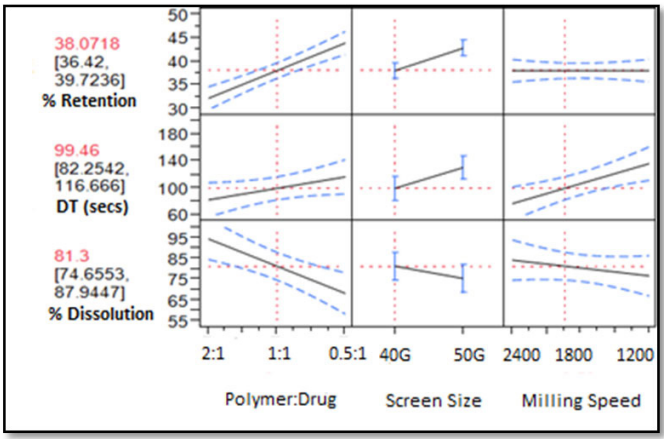

Figure 3: Prediction profiler for studied input and output variables.

Failure mode and effect analysis (FMEA)-Updated:

FMEA was updated based on DoE optimization studies results and risk was reduced to low from high or medium risk.

Table 11: Updated FMEA for manufacturing process for Pazopanib HCl Extrudates

Variable location	Variable	S	O	D	Updated RPN	Risk mitigation strategy
HME Formula	Polymer to drug ratio	4	3	1	12	Optimum level of polymer to drug ration finalized.
Milling	Screen size	4	3	1	12	Screen size (40G) finalized.
Milling	Milling speed	3	2	1	6	Milling speed can be kept as optimum i.e. 1800 rpm

S-Severity, O- Occurrence, D- Detectability, Risk priority number (RPN) = S × O × D

DISCUSSION

In 2007, Food and Drug Administration (FDA) published a guidance on defining a target product profile (TPP). The TPP provides a written statement of the overall intent of drug development program.[14] QTPP and CQAs were discussed initially to design and development of Pazopanib HCl extrudates (PZP-Ex). Process map was defined for preparation of extrudates using HME technique. Initially risk was identified for the formula and process variables using risk assessment tools i.e., heat map and FMEA. The assigned risk for each unit operations were mitigated for medium and high risks process steps based on the scientific knowledge gained during the product development and through experimental trials.

In present study, full factorial design was used for optimization of formula and process variables and total 10 experimental trials were executed. The DoE trials with responses were analysed in JMP software (version 16.0) through "fit Model" approach. The *p* value signifies that the model is significant or not. The *p* value was observed less than 0.05 for all the studied response variables i.e., percent retention on 40 # ASTM sieve, disintegration time and percent drug release in 15 min hence model was significant.

The sorted parameters and p-value are summarized for the studies responses (Table 10). The % dissolution was directly proportional to polymer level and this might be due to the fact that higher polymer to drug ratio will convert the crystalline drug into amorphous solid dispersion state. Milling screen size may impact on extrudates granulometry due to apertures size differences between 40G and 50G mesh. 40G screen has small apertures in comparison to 50G screen. Disintegration time is likely to impacted by the ratio of coarse to fine granules, hence 40G obtained granules shows the faster disintegration and percent drug release.

CONCLUSION

In this study, impact of input variables on studied responses for prepared Pazopanib HCl extrudates by HME technique were successfully optimized. The Pazopanib HCl API was embedded in Affinisol HPMC polymer along with using Poloxamer 188 as plasticizer. The main goal to carried out risk assessment for Pazopanib HCl extrudates are to reduce the process variations, probability failure rate and manufacturing process defects, thereby obtaining robust unit operations and enhancing manufacturing efficiencies. The polymer to drug ratio has significant impact on drug release and disintegration time of extrudates. The key elements of pharmaceutical QbD were included i.e., QTPP, process design and understanding, CQAs, prior scientific knowledge, risk elements (Heat map and FMEA), DoE screening, and control strategy. Based on the DoE screening study, critical process parameters such as polymer to drug ratio, milling screen size and milling speed were optimized and proposed as 2:1, 40G and 1800 rpm respectively.

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Authors' Contribution:

Gupta A conceptualised the research work. Also performed experimentation and analysis.

Dahima R performed the statistical data interpretation and contributed to manuscript writing.

Abbreviations: ANOVA: analysis of variance; BCS: biopharmaceutics classification system; CPPs: critical process parameters; CQAs: critical quality attributes; DoE: design of experiments; DPCQA: during production check quality assurance; FDA: food and drug administration; FFD: full factorial design; FMEA: failure mode and effect analysis; HME: hot melt extrusion HPLC: high performance liquid chromatography; ICH: international council for harmonisation of technical requirements for pharmaceuticals for

human use; IPQA: in process quality assurance; NSAID: non-steroidal anti-inflammatory drug; PAT: process analytical technology; Pazopanib HCl Extrudates: PZP-Ex; QbD: Quality by design; QbT: quality by testing; QRA: quality risk assessment; QTPP: quality target product profile; TPP: target product profile

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